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Docket No. GJE-21D2  
Serial No. 09/760,274Remarks

Claims 57-67 were pending in the subject application. By this Amendment, claims 57-62 have been amended, claims 63 and 65-67 have been canceled, and new claims 68-75 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 57-62, 64, and 68-75 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

An Advisory Action dated April 14, 2003 was received by the applicants. Submitted herewith is a Request for Continued Examination (RCE) in the subject application.

By this Amendment, the applicants have updated the cross-reference section at page 1 of the specification to indicate that U.S. patent application serial no. 09/043,061 is now abandoned.

The Office Action indicates that the priority document cannot be found in application serial no. 09/672,606. As indicated in the Claim of Priority under 35 U.S.C. §119 submitted November 14, 2001, a certified copy of Great Britain application no. UK 9518606.0 should be found in parent application serial no. 09/043,061. However, should it be necessary, the applicants will submit an additional certified copy of Great Britain application no. UK 9518606.0 in a subsequent communication for the Examiner's convenience.

The applicants gratefully acknowledge the Examiner's indication at page 4 of the Office Action that claims 57-58 and 60-67 have support in the subject specification as originally filed.

Claim 59 is rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants respectfully submit that claim 59 is sufficiently described in the subject specification. However, by this Amendment, the applicants have amended claim 59 to recite that the cells differentiate after transplantation. As indicated at page 5, lines 10-22, and page 9, lines 13-25, of the specification, post-mortem histological preparations showed that, once transplanted, the pluripotent cells have the appearance of differentiated cells, taking up a phenotype or phenotypes appropriate to the host's nervous system. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

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Claims 57-67 have been rejected under 35 U.S.C §112, first paragraph, as non-enabled by the subject specification. The Office Action indicates that the specification does not enable the administration of non-hippocampal pluripotent, nestin-positive, neuroepithelial cells that have been genetically modified so as to be conditionally immortal, in order to treat cognitive deficits caused by damage to areas of the brain other than the hippocampus. The applicants respectfully submit that the claims are fully enabled by the subject specification. However, by this Amendment, the applicants have amended claims 57-62 and added claims 68-75 in order to lend greater clarity to the claimed subject matter.

Claims 57 and 70 recite that the cognitive deficit is caused by damage to the hippocampus and that the pluripotent, nestin-positive, neuroepithelial cells are hippocampal cells. Support for the transplantation of hippocampal cells into the hippocampus can be found in Examples 1-9, pages 17-29, of the specification. The applicants gratefully acknowledge the Examiner's indication at page 7 of the Office Action that the enablement rejection as to the breadth of "animal" has been withdrawn, and the enablement of "mammals" has been acknowledged. As indicated in the previous Amendment dated September 30, 2002 and accompanying Expert Declaration under 37 CFR §1.132 by Dr. John Sinden, experimental data (submitted with Dr. Sinden's Expert Declaration) has been obtained confirming the efficacy of the pluripotent cells in treating primates, including marmosets and humans.

Claims 57 and 70 also recite that the pluripotent, nestin-positive, hippocampal neuroepithelial cells comprise a temperature-sensitive simian virus 40 (SV40) large T antigen gene. Support for cells possessing the temperature-sensitive SV40 large T antigen gene can be found at page 9, lines 5-13, of the specification. Claims 68 and 75 recite that the temperature-sensitive virus-40 large T antigen gene is under the control of an interferon-inducible H-2K<sup>b</sup> promoter. Support for claims 68 and 75 can be found, for example, at page 9, lines 5-13, of the subject specification.

Accordingly, in view of the foregoing remarks and amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §112, first paragraph.

Claims 57-67 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that the claims are not indefinite. However, as indicated in the

preceding paragraphs, the applicants have amended the claims in order to lend greater clarity to the claimed subject matter. Claims 57-62, 64, and 68-75 do not recite the phrases "conditionally immortal," "said transplantation," "but," "differentiate to replace, or compensate for, said lost or damaged brain cells," "*in vivo*," or "temperature-sensitive oncogene". Claims 62 and 74 recite that the damage is the result of hypoxia. Support for claims 62 and 74 can be found, for example, at page 2, lines 34-36, and page 10, lines 1-9, of the specification. Claims 57 and 69 recite that the pluripotent, nestin-positive, hippocampal neuroepithelial cells have a temperature-sensitive simian virus 40 large T antigen gene. The Office Action indicates that a copy of the Jat *et al.* publication (*Proc. Natl. Acad. Sci. USA*, June 1991, 88:5096-5100), which is cited at page 9, line 4, of the specification, was not available. A copy of the Jat *et al.* publication, which describes the simian virus 40 (SV40) large tumor (T) antigen (TA<sub>g</sub>) gene, is submitted herewith for the Examiner's consideration.

Accordingly, in view of the foregoing remarks and amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejection set forth under 35 U.S.C. §112, second paragraph.

Claims 57-60, 62, and 65-67 have been rejected under 35 U.S.C. §103(a) as being obvious over Netto *et al.* (*Behavioral Brain Res.*, 1993, 58:107-112) taken with Renfranz *et al.* (*Cell*, 1991, 66:713-729). In addition, claims 57-62 and 65-67 have been rejected under 35 U.S.C. §103(a) as being obvious over Netto taken with Renfranz in view of Rashid-Doubell (*Gene Therapy*, 1994, 1(1):S63) and White and Whittemore (*J. Chem. Neuroanatomy*, 1992, 5:327-330). The applicants respectfully submit that the cited references, when taken alone or together, do not teach or suggest the methods of the subject invention. However, by this Amendment, the applicants have amended the claims in order to lend greater clarity to the claimed subject matter.

As indicated in the preceding paragraphs, claims 57 and 69 now recite that the cognitive deficit is caused by damage to the hippocampus and that the pluripotent, nestin-positive, neuroepithelial cells are hippocampal cells. In addition, claim 57 has been amended to incorporate the subject matter of claim 63, *i.e.*, that the transplanted cells are human cells. New claim 69 recites the subject matter of claim 64, *i.e.*, that the cells are transplanted into a human. Support for treatment of humans and transplantation of human cells can be found, for example, at page 2, lines

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14-24, and page 13, lines 14-16, of the specification. Claims 63 and 64 were not included in the prior art rejections under 35 U.S.C. §103(a). The applicants respectfully submit that the cited references do not teach or suggest the methods of the subject invention as currently claimed.

Accordingly, in view of the foregoing remarks and amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Marked-Up Version of Substitute Paragraph  
Marked-Up Version of Amended Claims  
Copy of the Jat *et al.* (1991) publication

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**Marked-Up Version of Substitute Paragraph**

Please replace the paragraph found on page 1, line 2 of the specification with the following paragraph:

This application is a continuation application of USSN 09/672,606, filed September 28, 2000; which is a continuation application of USSN 09/043,061, filed March 12, 1998, now abandoned; which is a national stage application of PCT/GB96/02251, filed September 12, 1996.

**Marked-Up Version of Amended Claims****Claim 57 (Amended):**

A method of treating a cognitive deficit [in a mammal] caused by damage to the hippocampus of a mammal, said method comprising intracerebrally transplanting human pluripotent, nestin-positive, hippocampal neuroepithelial cells into said hippocampus of said mammal, [wherein said cells have been genetically modified to be conditionally immortal, wherein said cells are immortal prior to said transplantation but differentiate after said transplantation] wherein said human pluripotent, nestin-positive, hippocampal neuroepithelial cells comprise a temperature-sensitive simian virus 40 large T antigen gene, and wherein said [transplantation] transplanting improves cognitive function in said mammal.

**Claim 58 (Amended):**

The method of claim 57, wherein said [cognitive deficit is caused by damage to, or loss of, brain cells in said mammal, and wherein said transplanted cells differentiate to replace, or compensate for, said lost or damaged brain cells] damage comprises damage to, or loss of, brain cells in said hippocampus of said mammal.

**Claim 59 (Amended):**

The method of claim 57, wherein said human pluripotent, nestin-positive, hippocampal neuroepithelial cells differentiate [into neurons and glial cells *in vivo*] after said transplanting.

**Claim 60 (Amended):**

The method of claim 57, wherein said human pluripotent, nestin-positive, hippocampal neuroepithelial cells are cells of a clonal cell line.

**Claim 61 (Amended):**

The method of claim 57, [wherein said cells are obtained by culturing said cells in serum-free medium] wherein said method further comprises culturing said human pluripotent, nestin-positive, hippocampal neuroepithelial cells in serum-free medium prior to said transplanting.

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Claim 62 (Amended):

The method of claim 57, wherein said [cognitive deficit] damage is the result of hypoxia.